## Q&A column

### Editor: Frederick L. Kiechle, MD, PhD

Submit your pathology-related question for reply by appropriate medical consultants. CAP TODAY will make every effort to answer all relevant questions. However, those questions that are not of general interest may not receive a reply. For your question to be considered, you must include your name and address; this information will be omitted if your question is published in CAP TODAY.

# Q. Should phosphate analysis be added to the comprehensive metabolic panel, especially given the test's usefulness in distinguishing various bone disorders?

A.July 2023—Phosphate represents one percent of total body weight and has a normal reference range of 2.5 to 4.5 mg/dL. The reference range is highest in infants (4.5–8.3 mg/dL) and decreases with age. The majority of phosphate in the skeleton is in the form of hydroxyapatite crystals or amorphous calcium phosphate.<sup>1</sup> There are two forms of phosphate in serum: dihydrogen phosphate ( $H_2PO_4$ ) and monohydrogen phosphate ( $HPO_4$ ).<sup>1</sup> The **table** illustrates biochemical changes in bone diseases.<sup>2,3,4</sup>

Three hormones regulate phosphate homeostasis: vitamin D (calciferol) or D2 (ergocalciferol) and D3 (cholecalciferol), which are processed by the liver to 25-hydroxy vitamin D; parathyroid hormone; and fibroblast growth factor 23. FGF23 is produced by osteocytes or osteoblasts and consists of 251 amino acids with a signal peptide comprising 24 amino acids.<sup>3,5</sup> It inhibits renal reabsorption of phosphate after binding to the FGFR1-Klotho complex.<sup>6</sup> Alpha-Klotho serves as a co-receptor.<sup>6</sup> Tumor-induced osteomalacia (TIO) is a rare paraneoplastic disorder caused by benign phosphaturic mesenchymal tumors that secrete FGF23 and can present anywhere in the body. TIO is diagnosed, on average, 2.9 years after the onset of symptoms, and the underlying tumor is identified, on average, 5.4 years after symptom onset. Therefore, a chronically low phosphate found via screening may be the only clue that points to the onset of TIO.<sup>2,3,5,6</sup>

Osteopenia is a condition in which bone mineral density is lower than the normal peak density but not low enough to be considered osteoporosis.<sup>4</sup> Several diseases or therapies have been associated with increased bone fragility and fractures, including diabetes mellitus type 1<sup>7</sup> and type 2,<sup>8</sup> hormone treatments for transgender transition (puberty blocks and gender-affirming therapy),<sup>9</sup> and subclinical thyroid dysfunction with a thyrotropin level of less than 0.56 mIU/L.<sup>10</sup>

There are a variety of other disorders associated with hyperphosphatemia or hypophosphatemia that would benefit from a screening phosphate determination.<sup>11,12</sup> It is clearly time to reassess whether to include serum phosphate in the comprehensive metabolic panel.

#### Biochemical changes in bone disease

Bone disease	Phosphate	Calcium	PTH	ALP	FGF23	Vitamin D
Osteopenia, premature infants	D	D		L		
Osteoporosis	NC	NC	NC	NC		
Primary hyperparathyroidism	D	I	1	I		
Malignant hypercalcemia	NC	I	D	1		
Osteomalacia						
Rickets, vitamin D deficiency	D	D	I	I		V
X-linked hypophosphatemic rickets	D	NC	NC or I	1	1	D or NC
Autosomal dominant hypophosphatemic rickets	D	NC	NC	1		D
Autosomal recessive hypophosphatemic rickets, type 2	D	NC	NC	I	1	
Tumor-induced osteomalacia or oncogenic osteomalacia	D	D	I	t	l	

D, decreased; I, increased; NC, no change; PTH, parathyroid hormone; ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23; V, variable.

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#### Q. Is it important to fast before a lipid panel?

A.Cholesterol and other lipids are transported in plasma by various lipoprotein particles, including low-density lipoproteins (LDL) and high-density lipoproteins (HDL). While HDL is non-atherogenic and may even be protective, an elevated plasma concentration of the cholesterol carried in LDL (LDL-C) is a well-described risk factor for atherosclerotic cardiovascular disease (ASCVD).

Clinical practice guidelines recommend a target LDL-C level of <100 mg/dL for the primary prevention of ASCVD.<sup>1</sup> Importantly, LDL-C is not typically measured directly in clinical practice. It is more often calculated using the Friedewald formula (calculated LDL-C = total cholesterol – HDL-C – triglycerides/5). Fasting values historically have been recommended to ensure that triglycerides are <400 mg/dL and that accurate calculated LDL-C values are obtained. However, recent studies have confirmed that nonfasting calculated LDL-C values have worth in predicting ASCVD.<sup>2,3</sup> Yet it is now widely recommended that nonfasting non-HDL-C be used for patient management in the general population.

Non-HDL cholesterol, which is calculated by subtracting HDL-C from total cholesterol, encompasses all atherogenic lipoprotein particles and more effectively predicts the risk of major cardiovascular events, including coronary artery disease and stroke, than does LDL-C.<sup>4,5</sup> Additionally, in contrast to LDL-C and triglyceride levels, total cholesterol and HDL-C levels are minimally affected by fasting status.<sup>2,3</sup> Therefore, non-HDL-C can be reliably calculated from nonfasting specimens and the specimens of people with hypertriglyceridemia.

Although cholesterol-reducing agents originally targeted calculated LDL-C, they are now also recommended for managing non-HDL-C in the primary and secondary prevention of ASCVD.<sup>6</sup> The target non-HDL-C levels for primary and secondary prevention are <130 mg/dL and <100 mg/dL, respectively. These cutoffs are suitable for fasting and nonfasting specimens.<sup>7</sup>

Implementation of non-HDL-C testing in the clinical laboratory involves a simple calculation and no additional assays, and it supports patient care by being convenient for all and ideal for those in whom fasting carries additional risk. Measurement of non-HDL-C is thus simple, robust, and clinically effective, and clinical laboratories should make it widely available for assessing ASCVD risk.

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